Original Article

Staphylococcal Blood Stream Infections: Epidemiology, Resistance Pattern and Outcome at a Level 1 Indian Trauma Care Center

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ABSTRACT

Purpose: Blood stream infection (BSI)/bacteremia is a potentially life threatening infection and are associated with a high crude mortality. Coagulase negative Staphylococcus (CONS) and *Staphylococcus aureus* are the most commonly isolated gram positive bacteria from blood culture samples. While *S. aureus* is a known pathogen causing BSIs, CONS are considered to be common contaminants of blood culture. Of late many studies have challenged this traditional viewpoint. The aim of this study was to determine the epidemiology and significance of *Staphylococcus aureus* and CONS bacteremia, their resistance patterns and associated mortality in critically ill trauma patients admitted to a level 1 trauma center.

Materials and Methods: The study was conducted from January 2009 to June 2011. All patients from whose blood samples yielded a *S. aureus* or CONS on culture were included in this study. A detailed history was obtained and follow-up of the patients was done. The isolates of Staphylococci were identified to species level. Antibiotic susceptibility was performed by the disc diffusion method and VITEK-2 system.

Results: During this 30 month period, total of 10,509 blood samples were received from 2,938 patients. A total of 1,961 samples taken from 905 patients were positive for one or more pathogens. *S. aureus*/CONS were isolated from 469 samples from 374 patients. Crude mortality amongst the patients having Staphylococcal BSI was 25% (94/374).

Conclusion: Staphylococcal blood stream infections are a leading cause of morbidity and mortality.

Key words: Bacteremia, coagulase negative staphylococcus, methicillin resistant *Staphylococcus aureus*, mortality, *Staphylococcus aureus*

INTRODUCTION

Blood stream infection (BSI)/bacteremia is a potentially life threatening infection. They can be community acquired or hospital acquired infections. Hospital acquired BSIs are associated with higher morbidity and mortality, along with increased overall health care costs. BSIs have an associated crude mortality of about 35% ranging from 12% to 80%.[1] BSIs can be primary or secondary BSI, based on the source of origin. Primary/intravascular BSI originates from the cardiovascular system itself; while, some other infectious focus in the body gives rise to the secondary/extra vascular BSI. Coagulase negative Staphylococcus (CONS) and *Staphylococcus aureus* are the most commonly isolated gram positive bacteria from blood culture samples.[2] *S. aureus* is a major cause of BSIs, both in the hospital and the community setting.[3,4] The case fatality (CF) associated with *S. aureus* bacteremia (SAB) remains high, ranging from 7% to 39%.[5]

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Studies have found gram positive organisms to be the major contributors of BSIs. In the past few decades, CONS have emerged as important causes of bacteremia. CONS are present on skin as commensal flora, therefore presence of CONS in blood is usually considered to be due to blood culture contamination,

especially if a single culture is positive. CONS bacteremia has traditionally been considered significant only when it is isolated multiple times. Recent studies have challenged this hypothesis and tried to establish the significance of single blood culture positive for CONS. Therefore, we conducted this study to ascertain the clinical significance of Staphylococcal bacteremia, especially with respect to the associated mortality. Our objective was to ascertain the clinical significance of CONS bacteremia and compare its clinical profile and outcome with bacteremia caused by *S. aureus*, in a setting of trauma patients. We hypothesized that in severely traumatized patients, on multiple life support devices, the significance of bacteremia due to *S. aureus* or CONS would be low, in terms of attributable mortality. Since all medico-legal trauma patients are subjected to autopsy, we tried to evaluate the contribution of BSI due to *S. aureus*/CONS to a fatal outcome in such patients.

MATERIALS AND METHODS

Setting

The study was conducted at the JPNA Trauma Center, which is the first level-1 Trauma Center of India, where patients from all over India are referred. The Trauma Center is a part of the AIIMS hospital, which itself is a 2,200 bedded, tertiary, referral and teaching hospital of India. Of the total 152 beds in the Trauma Center, 32 are ICU beds. A total of 6 nurses function as full time Hospital Infection Control Nurses (HICNs). We have initiated a targeted surveillance of device associated infections (VAP, CR-BSI, CA-UTI) and clinical sepsis, based on the definitions proposed by CDC's NHSN.[6]

The study was conducted from January 2009 to June 2011.

All patients whose blood samples yielded *S. aureus* or CONS were included in the study. The isolates were identified on the basis of standard microbiological methods. In addition, each isolate was identified by the VITEK 2 system using the GP-ID cards. We analyzed data regarding blood cultures positive for *Staphylococcus* spp. (CONS and *S. aureus*). The data was separately analyzed for patients with blood culture positive for *Staphylococcus aureus* isolates and CONS presenting with/without clinical signs or symptoms of septicemia. The aim of this study was to determine the mortality associated with Staphylococcus bacteremia and to determine the clinical significance of single blood culture positive for CONS. We also looked at the methicillin resistance profile and mortality associated with these BSI and tried to determine the probable cause of death.

Antimicrobial susceptibility testing

The antimicrobial susceptibility of bacterial isolates was done by the disc diffusion method according to the CLSI guidelines.[7-9] *Staphylococcus aureus* ATCC 25923, *Escherichia coli* ATCC 25922 and *Pseudomonas aeruginosa* ATCC 27853 were taken as control strains. For gram positive cocci, the following antibiotics were tested: Ampicillin (10 μg), vancomycin (30 μg), clindamycin (2 μg), erythromycin (15 μg), linezolid (30 μg), tetracycline (30 μg), teichoplanin (30 μg), amplicillin/sulbactam (10/10 μg), penicillin (10 units), rifampicin (5 μg), amoxicillin/clavulinic acid (20/10 μg), amikacin (30 μg), netilmicin (30 μg), gentamycin (30 μg), ciprofloxacin (5 μg), co-trimoxazole (25 μg), cefoxitin (30 μg), levofloxacin (5 μg) and oxacillin (1 μg). The interpretative zone diameters used were as per CLSI recommendations.[7-9]

Apart from this, the minimum inhibitory concentrations (MICs) were determined for all bacteria and Candida isolates by the Vitek 2 system (using AST GP/GN/YST cards).

BSI was defined as per CDC's definition. The definition of primary and secondary BSI was defined as per standard definition. For each positive culture, an intensive effort was made to trace the source of infection. Since tracheal aspirate and urine samples are taken from each patient. Moreover, an intensive surveillance for VAP, UTI and SSI is done at our center. This was used to accurately diagnose secondary BSI.

All trauma victims who had medico-legal causes of trauma and had fatal outcome are subjected to autopsy. Thus, for all the patients in our series whose autopsy was done, the clinical and autopsy cause of death was recorded. For all other fatal cases, only the clinical cause of death was recorded. The attributable cause of death due to Staphylococcal bacteremia was ascertained by noting the cause of death, the time interval between a positive culture and fatal outcome and other associated infections like VAP, wound infections, meningitis etc., due to some other pathogens.

RESULTS

During this 30 month period, a total of 10,509 blood samples were received from 2,938 patients. A total of 1,961 samples taken from 905 patients were positive for one or more pathogens. *S. aureus* and CONS were isolated from 469 samples from 374 patients. Overall, 53% of isolates were *S. aureus* (248/469); CONS (221/469) contributed for the remaining 47%.

The crude mortality amongst these patients was 25% (94/374). Autopsy was done for 76 patients to determine the cause of death. A total of 51 of 76 (67%) of deaths were due to septicemia as determined on autopsy. However, in our opinion, in 38 of these 51 (75%) patients, Staphylococcal BSI alone cannot be associated with these deaths due to various confounding factors like prolonged time gap between culture positivity and death and presence of other concomitant ante-mortem infections like VAP, meningitis or abdominal sepsis. Therefore, in our opinion only 17% (13/76) deaths were attributable to Staphylococcal septicemia [Tables 1-3].

A total of 248 blood culture samples from 181 patients were positive for *S. aureus*. A total of 185 episodes of *S. aureus* BSI occurred in these 181 patients. *S. aureus* was isolated from central venous catheter tips during six episodes. Secondary bacteremia was seen in 8 (4%) patients. Of these, 7 had *S. aureus* isolated from infected wounds and one had VAP, with tracheal aspirate positive for *S. aureus*. A total of 146 (59%) of the *S. aureus* isolates recovered from 185 episodes were methicillin resistant. Of the 181 patients who had *S. aureus* bacteremia, 52 of them (29%) had a fatal outcome. Autopsy was performed in 43 patients to determine the cause of death, where 12 (28%) were found to have died due to septicemia.

A total of 22 cultures yielded CONS. However, only 22 episodes of clinically significant CONS bacteremia were seen in 22 patients. All these patients had two or more blood cultures positive for the same isolate. A total of 14 (29%) of the CONS isolates were methicillin resistant. Of the 22 patients who had CONS bacteremia, 3 (14%) had a fatal outcome. The same organism was isolated from central venous catheter in two and from peripheral venous catheter in one patient.

A total of 173 blood cultures from 171 patients were considered to be clinically insignificant based on our defining criteria. Methicillin resistance was seen in 78% (134/173) of these isolates. Of these 171 patients, 39 (23%) had a fatal outcome. Autopsy findings revealed that only one of these 31 deaths (3%) was related to septicemia.

DISCUSSION

Staphylococcal blood stream infections are associated with high mortality rates. In our study, we found overall 29% crude mortality amongst patients having *Staphylococcus aureus* BSI. It corroborates well with various studies conducted by Conterno *et al.*,[10] Kanafani *et al.*[11] and Forsblom *et al.*[5] who described a range of 7% to 39%. Wisplinghoff *et al.*[12] reported 25.4% deaths. Ribas *et al.*[13] from Brazil reported (39.2%) mortality in their set up.

Methicillin resistance in *S. aureus* has been increasing over the years. We observed that at our center, 59% of *S. aureus* strains causing BSI were MRSA. Parameswaran *et al.*[2] found MRSA accounted for 26.7% of patients with CRBSI. Wisplinghoff *et al.*[12] found that 41% of their strains were MRSA. The MRSA strains found in studies by Kaech *et al.*[14] (2%), Lautenschlager *et al.*[15] (34%), and Wyllie *et al.*[16] (50%) are shown in the parentheses, respectively. It therefore calls in for better vigilance and implementation of more effective MRSA screening programs complemented with improved infection control practices.

In various studies, Methicillin resistance was found as an independent predictor of mortality. Clinical outcome of a patient depends upon multiple mechanisms and multiple factors viz. age, co-morbid conditions, hemodynamic status, immunosuppression, infecting organism, timely diagnosis and treatment etc., which play a role in the downward trend of events in patients with BSI. Death is the end result of the downhill course in the clinical status of a patient.

Table 1: Demographic profile of patients with Staphylococcal BSI

Organism	Patients	Episodes	Samples	Methicillin resistant	Mortality
S. aureus	181	185	248	146	52
CONS clinically significant	22	22	48	14	3
CONS clinically non- significant	171	173	173	134	39

BSI: Blood stream infection, CONS: Coagulase negative Staphylococcus

Table 2: Cause of death in our patient population

Organism	Cause of mortality					
	Mortality	Injury (%)	Autopsy not done (%)	Septicemia unrelated (%)	Septicemia related (%)	Other causes (%)
S. aureus	52	11 (21)	9 (17)	19 (37)	12 (23)	1 (2) Pneumonia
CONS clinically significant	3	1 (33)	1 (33)	1 (33)	-	-
CONS clinically non- significant	39	10 (26)	8 (21)	18 (46)	1 (2)	2 (5) Abdominal infection

CONS: Coagulase negative Staphylococcus

Table 3: Resistance profile of all Staphylococcal isolates

Antibiotic	No. of resistant isolates (%)		
	Staph. aureus *n*=248	CONS (significant) *n*=48	CONS (non-significant) *n*=173
Penicillin	241 (97)	48 (100)	171 (99)
Ampicillin	236 (95)	46 (96)	168 (97)
Oxacillin	146 (59)	14 (29)	134 (78)
Cefoxitin	146 (59)	14 (29)	134 (78)
Amoxicillin/Clavulanic acid	172 (69)	35 (73)	137 (79)
Ampicillin/Sulbactam	166 (67)	32 (67)	135 (78)
Erythromycin	157 (63)	37 (77)	131 (76)
Clindamycin	152 (61)	37 (77)	130 (75)
Vancomycin	0 (0)	0 (0)	0 (0)
Teicoplanin	0 (0)	0 (0)	0 (0)
Linezolid	0 (0)	0 (0)	0 (0)
Netilmicin	33 (13)	9 (19)	27 (16)
Cotrimoxazole	181 (73)	37 (77)	129 (75)
Tetracycline	78 (32)	12 (25)	53 (31)
Rifampicin	67 (27)	8 (17)	52 (30)
Ciprofloxacin	64 (26)	14 (29)	47 (27)
Levofloxacin	57 (23)	10 (21)	34 (20)
Amikacin	243 (98)	43 (90)	168 (97)
Gentamycin	243 (98)	46 (96)	168 (97)

CONS: Coagulase negative Staphylococcus

Studies by Kaech *et al.*[14] have shown 2% of MRSA prevalence in bacteremia patients with crude mortality ranging from 13% in nosocomial and 26% in community acquired *Staphylococcus aureus* bacteremia, respectively. However, it has been observed in studies conducted by Kaech *et al.*,[14] Jensen *et al.*[17] and Cunney *et al.*[18] that the mortality caused by community acquired *Staphylococcus aureus* bacteremia was greater as compared to nosocomial cases, probably due to earlier detection and commencement of appropriate therapy of BSI in a hospital setting as compared to community acquired infections.

In our study, 59% of the *Staphylococcus aureus* bacteremia cases were caused by MRSA strains. Mortality was seen in 31% (45/146) of bacteremia caused by MRSA strains as compared to 18% mortality (7/39) observed in MSSA bacteremia. Wyllie *et al.*[16] have found in their study that 50% of the Staphylococcal bacteremia cases were caused by MRSA strains and the overall mortality was 29%. The mortality caused by MRSA strains was 34% while mortality due to bacteremia caused by MSSA strains was 27%. Laupland *et al.*[19] have found 11% MRSA strains with 39% mortality as compared to 24% mortality in MSSA bacteremia. Both Wyllie *et al.*[16] and Laupland *et al.*[19] did not find any significant difference between mortality rates in patients suffering from bacteremia caused by either MRSA or MSSA strains, although both the study groups found that over the years the Staphylococcal bacteremia was caused proportionately more frequently by MRSA strains. This may be a reflection of selective antibiotic pressure over the years.

In our study, 59% of the Staphylococcal blood stream infections were caused by MRSA strains and overall crude mortality was 29%. Although, the methicillin resistance is higher in our study as compared to various studies conducted in U.S., U.K., Europe, but, the mortality rates are almost similar. We did not observe any proportionate increase in crude mortality rates as one would expect in comparison to these studies from west. Therefore, crude mortality rates many times can be misleading and may project the infecting resistant organism as having high virulence while there are various other underlying factors leading to adverse outcomes in these patients having BSI. We therefore believe that the prognosis of Staphylococcal BSI should be based on a more holistic clinical appraisal of the patients rather than biasing our thought process with the resistance profile of the causative organism.

Crude mortality was higher in patients having CONS isolated from blood single time as compared to those where CONS was isolated multiple times from blood (23% v/s 14%). The difference however was not statistically significant ($P = 0.419$). Our observations are in complete agreement of the findings of Favre *et al.*[20] who also reported a higher mortality in patients with single blood culture positive for CONS as compared to patients with multiple blood cultures positive (15.3% v/s 7.0% at day 14 and 20.8% v/s 11.3% at day 28). However, they also did not find a significant difference in mortality of both groups. We fully support their recommendation that a single blood culture positive for CONS in presence of clinical manifestations of sepsis should be considered clinically relevant and not simply disregarded as contaminants.

Limitations of the study

Trauma patients are relatively young patients with few co-morbid conditions. Mortality in this group is dependent on a number of factors and the most important of them is the severity of injury sustained at the time of trauma and the chances of microbial infections due to loss of normal epithelial barriers and penetrating injuries remain high. These patients have to be monitored invasively, undergo multiple surgeries and have a prolonged intra-hospital stay; all of these factors predispose them to various hospital acquired infections.

Therefore, it is sometimes difficult to attribute their mortality to a single cause as most often there are multiple factors involved in the downhill course to death in these

patients. Hence, our attribution of death in these patients having Staphylococcal bloodstream infections may not be totally appropriate.

Moreover, the number of patients having CONS bacteremia in presence or absence of clinical features of sepsis was not good enough to draw meaningful conclusions. In future, better studies with larger number of study subjects can be planned to add more power to the study and hence validate the results.

CONCLUSIONS

Staphylococcus spp. is an important cause of bloodstream infections in our settings and is associated with significant mortality and morbidity. The significance of both *Staphylococcus aureus* and CONS bacteremia should be evaluated better in light of clinical profile of the patient. Therefore, clinical correlation is a sine qua non in determining the significance of isolation of any bacteria from blood culture samples. High rates of methicillin resistance in our center calls for better screening and infection control practices in the future.

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